1. AMENDMENT

1.1 IN THE CLAIMS:

1. (Currently Amended) A growth factor composition comprising: a polypeptide of the TGF-β superfamily other than bFGF, and a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD, and a solvent selected from the group consisting of water and aqueous buffer solutions, said composition being capable of promoting angiogenesis ~~without inducing osteogenesis~~ when administered to a living subject at a site in need of such angiogenesis.

2. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is a polymer of N-vinyl-2-pyrrolidone.

3. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is a homopolymer of N-vinyl-2-pyrrolidone.

4. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is povidone.

5. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer solubilizes said growth factor.

6. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is water soluble.

7. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is provided at a concentration of from about 0.1% weight/volume to about 70% weight/volume.

8. (Original) The composition of claim 1, wherein said vinyl pyrrolidone is provided at a concentration of from about 0.1% weight/volume to about 50% weight/volume.

9. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is provided at a concentration of from about 0.1% weight/volume to about 55%.

10. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is provided at a concentration of from about 0.5% weight/volume to about 2.5%.

11. (Original) The composition of claim 1, wherein said vinyl pyrrolidone polymer is provided at a concentration of about 1% weight/volume.

12. (Original) The composition of claim 1, wherein said polypeptide of the TGF-β superfamily comprises a Bone Morphogenetic Protein.

13. (Previously Presented) A growth factor composition comprising:

at least two growth factors selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β3, and FGF-1;

a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20kD; and

a solvent selected from the group consisting of water and aqueous buffer solutions, said composition being capable of promoting angiogenesis when administered to a living subject at a site in need of such angiogenesis.

14. (Previously Presented) A growth factor composition comprising:

a polypeptide of the TGF-β superfamily,

a growth factor selected from the group consisting of IGF-1, EGF, HGF, TGF-α, and PDGF,

a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20kD, and

a solvent selected from the group consisting of water and aqueous buffer solutions, said composition being capable of promoting angiogenesis when administered to a living subject at a site in need of such angiogenesis.

15. (Previously Presented) A growth factor composition comprising:

BMP-2, BMP-3, BMP-7, TGF-β1, TGF-β2, and FGF;

a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20kD; and

a solvent selected from the group consisting of water and aqueous buffer solutions, said composition being capable of promoting angiogenesis when administered to a living subject at a site in need of such angiogenesis.

16. (Currently Amended) A method for inducing angiogenesis in a patient comprising: providing a growth factor composition comprising a polypeptide of the TGF-β superfamily other than bFGF, and a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD and a solvent selected from the group consisting of water and aqueous buffer solutions; and administering the growth factor composition to a patient in need of angiogenesis, such that angiogenesis is induced ~~without induction of osteogenesis~~.

17. (Original) The method of claim 16, wherein the patient is human.

18. (Original) The method of claim 16, wherein said step of administering comprises injecting the composition into the patient's body.

19. (Previously Presented) The method of claim 16, wherein said step of administering comprises injecting the composition into the patient's heart.

20. (Previously Presented) A method for inducing angiogenesis in a patient in need thereof comprising:

providing a growth factor composition comprising a polypeptide of the TGF-β superfamily, a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD, and a solvent selected from the group consisting of water and aqueous buffer solutions; and

administering the growth factor composition to said patient subcutaneously.

21. (Previously Presented) A method for inducing angiogenesis in a patient in need thereof comprising:

providing a growth factor composition comprising a polypeptide of the TGF-β superfamily, a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD, and a solvent selected from the group consisting of water and aqueous buffer solutions; and

administering the growth factor composition to said patient intramuscularly.

22. (Previously Presented) A method for inducing angiogenesis in a patient in need thereof comprising:

providing a growth factor composition comprising a polypeptide of the TGF-β superfamily, a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD, and a solvent selected from the group consisting of water and aqueous buffer solutions; and

administering the growth factor composition to said patient intravenously.

23. (Original) A method for treating ischemic tissues, comprising: providing a growth factor composition comprising a polypeptide of the TGF-β superfamily and a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD and a solvent selected from the group consisting of water and aqueous buffer solutions; and administering the growth factor composition to the ischemic tissue.

24. (Original) The method of claim 23, wherein the ischemic tissue is myocardial tissue.

25. (Original) The method of claim 24, wherein said step of administering comprises injecting the composition into the myocardial tissue.

26. (Original) The method of claim 25, wherein the composition is a liquid having a viscosity of less than about 3 cP.

27. (Original) The method of claim 25, wherein the composition is a liquid having a viscosity of less than about 2.5 cP.

28. (Original) The method of claim 25, wherein the composition is a liquid having a viscosity of less than about 2 cP.

29. (Original) The method of claim 25, wherein the composition is a liquid having a viscosity of less than about 1.5 cP.

30. (Currently Amended) A method of promoting soft tissue regeneration in a living subject, comprising: providing a growth factor composition comprising a polypeptide of the TGF-β superfamily, other than bFGF, and a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD and a solvent selected from the

group consisting of water and aqueous buffer solutions; and administering the growth factor composition to the soft tissue, such that angiogenesis is induced at said site ~~without induction of osteogenesis~~.

31. (Currently Amended) A method for increasing the bioavailability of a growth factor at a site where soft tissue regeneration ~~without induction of osteogenesis~~ in a living subject is desired, comprising the steps of: providing said growth factor comprising a protein of the TGF-β superfamily, other than bFGF, disposed in an aqueous medium comprising a solvent selected from the group consisting of water and aqueous buffers; adding a vinyl pyrrolidone polymer to the medium; and administering said medium comprising said growth factor and said vinyl pyrrolidone polymer to said site, such that angiogenesis is induced at said site ~~without induction of osteogenesis~~.

32. (Previously Presented) A method for inducing angiogenesis comprising:

providing a composition containing a mixture of bone-derived growth factors and a carrier comprising a vinyl pyrrolidone polymer; and

administering said composition directly to an ischemic site in an individual in need of angiogenesis.

33. (Previously Presented) The method of claim 32 wherein the amino acid content of said mixture of bone-derived growth factor comprises:

about 20-25 mole% acidic amino acids (Asp(+Asn) and Glu(+Gln)),

about 10-15 mole% hydroxy amino acids (Ser and Thr),

about 35-45 mole% aliphatic amino acids (Ala, Gly, Pro, Met, Val, Ile and Leu),

about 4-10 mole% aromatic amino acids (Tyr and Phe), and

about 10-20 mole% basic amino acids (His, Arg and Lys).

34. (Previously Presented) The method of claim 32 wherein the amino acid content of said mixture of bone-derived growth factor comprises:

about 23.4 mole% acidic amino acids (Asp(+Asn) and Glu(+Gln)),

about 13.5 mole% hydroxy amino acids (Ser and Thr),

about 40.0 mole% aliphatic amino acids (Ala, Gly, Pro, Met, Val, Ile and Leu),

about 6.8 mole% aromatic amino acids (Tyr and Phe), and

about 16.6 mole% basic amino acids (His, Arg and Lys).

35. (Previously Presented) The method of claim 32 wherein about 60% of the protein content of said bone-derived growth factor mixture is histones, ribosomes and growth factors.

36. (Previously Presented) The method of claim 32 wherein said composition comprises a synergistic combination of bone-derived growth factors with respect to enhancing proliferation, migration and/or differentiation processes essential to angiogenesis, compared to that obtained with a single bone growth factor.

Please add the following new claims, 37-49:

37. (New) A method for inducing angiogenesis in a patient, said method comprising the step of providing to a patient in need of angiogenesis, the growth factor composition of any one of claims 13 to 15.

38. (New) The method of claim 37, wherein said patient is human.

39. (New) The method of claim 37, wherein said step of providing comprises injecting said growth factor composition into said patient's body.

40. (New) The method of claim 37, wherein said step of providing comprises injecting said growth factor composition into said patient's heart.

41. (New) The method of claim 37, wherein said step of providing comprises administering said growth factor composition to said patient subcutaneously.

42. (New) The method of claim 37, wherein said step of providing comprises administering said growth factor composition to said patient intramuscularly.

43. (New) The method of claim 37, wherein said step of providing comprises administering said growth factor composition to said patient intravenously.

44. (New) A method for treating ischemic tissue, said method comprising the step of providing to a patient in need thereof, the growth factor composition of any one of claims 13 to 15.

45. (New) The method of claim 44, wherein said ischemic tissue is myocardial tissue.

46. (New) The method of claim 44, wherein said step of providing comprises injecting said growth factor composition into said ischemic tissue.

47. (New) The method of claim 44, wherein said growth factor composition is a liquid having a viscosity of less than about 3 cP.

48. (New) A method of promoting soft tissue regeneration in a living subject, said method comprising the step of providing to a patient in need thereof, the growth factor composition of any one of claims 13 to 15.

49. (New) A method for increasing the bioavailability of a growth factor at a site where soft tissue regeneration in a living subject is desired, said method comprising the step of: providing to a site where soft tissue regeneration in a patient in need thereof is desired, the growth factor composition of any one of claims 13 to 15.

2. RESPONSE

2.1 STATUS OF THE CLAIMS

Claims 1-35 were pending at the time of the instant Action.

Claims 13-15, 20-29 and 32-36 have been allowed.

Claims 1, 16, 30, and 31 have been amended herein.

Claims 37-49 have been newly added herein.

Claims 1-49 now remain pending in the case.

2.2 SUPPORT FOR THE CLAIMS

Support for each of the claims as amended herein is provided by the Specification, drawings, and original claims as filed. Applicants certify that no new matter has been introduced as a result of the accompanying amendment. Newly added method claims 37-49 based on the previously allowed composition claims 13-15, have been added, and have been indicated by the Examiner in the recent interview to be allowable.

2.3 EXAMINER INTERVIEW

Applicants appreciate the extensive Interview conducted in the Office on July 15, 2004 with Examiner Jeffrey Russel and Applicants' new undersigned representative, Dr. Mark D. Moore, to discuss the pending claims, and to address the clarity and prior art issues which remained with respect to certain of the pending claims. As stated on the Interview Summary provided by the Office, during this interview, all claims were discussed, as well as all rejections and prior art. Applicants concur with Examiner Russel's suggestion with respect to the clarity issues concerning deletion of the phrase "without inducing osteogenesis" in claims 1, 16, 30, and 31, which Applicants have now done, to more particularly point out and distinctly claim

Applicants' invention. Applicants and their new representative also appreciate the helpful suggestions of the Examiner to overcome the rejection of certain claims under Section 103 of the Statutes by limitation of the claimed compositions to exclude bFGF to avoid potential obviousness issues with respect to the cited art.

Applicants appreciate the Examiner's finding that all pending claims were free of any rejections under Sections 101 and 102 of the Statutes, and appreciate the Examiner's helpfulness in suggesting particular claim language to more particularly point out and to improve the clarity of the few remaining claims which had rejections under either Sections 112 or 103.

As discussed in the Interview Summary of record, Applicants have also added method claims based upon the allowed composition claims (13-15), as new claims 37-49, and believe that these are fully allowable.

Mindful of the Applicants' recent change-of-counsel in this application, and in efforts to secure an economically-expedient allowance of the pending claims, Applicants' representative also appreciates the Examiner's availability for the recent interview, and his helpful suggestion of appropriate claim language to provide expedient allowance of the pending claims.

Applicants now believe that Examiner Russel will concur that all pending claims are allowable in view of the prosecution history and in view of the detailed and enabling disclosure of the present specification, in light of the amendment and remarks herein.

2.4 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, 1ST PARAGRAPH, IS OVERCOME

Claims 1-12, 16-19, and 30-31 were rejected under 35 U. S. C. § 112, 1st paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse; however, in the interest of expedient prosecution of the pending claims to allowance, and mindful of economic concerns and patent term issues,

Applicants have amended claims 1, 16, 30, and 31, to effectively incorporate the suggestion of Examiner Russel during the recent Interview to more particularly point out and distinctly claim the invention. Examiner Russel has indicated that the amended claim language is sufficient to obviate the rejection under this section of the Statutes. As such, Applicants respectfully request that the rejection under §112, 1st paragraph, be withdrawn.

2.5 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, 2ND PARAGRAPH, IS OVERCOME

Claims 1-12, 16-19, and 30-31 were also rejected under 35 U. S. C. § 112, 2nd paragraph, as allegedly be indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is essentially for the same reasons as stated in Section 2.4 above.

Applicants respectfully traverse; however, as mentioned above, in the interest of expedient prosecution of the pending claims to allowance, and mindful of economic concerns and patent term issues, Applicants have amended claims 1, 16, 30, and 31, to effectively incorporate the suggestion of Examiner Russel during the recent Interview to more particularly point out and distinctly claim the invention. In view of this clarification, Applicants now respectfully request that the rejection under §112, 2nd paragraph, be withdrawn.

2.6 THE OBJECTION TO CLAIM 12 UNDER 37 C. F. R. § 1.75(C) IS OVERCOME

Claim 12 was objected to under 37 C. F. R. § 1.75(c), as allegedly be of improper dependent form for failing to further limit claim 1. This rejection is essentially for the same reasons as stated in Sections 2.4 and 2.5 above.

Applicants respectfully traverse; however, as mentioned above, in the interest of expedient prosecution of the pending claims to allowance, and mindful of economic concerns and patent term issues, Applicants have amended claim 1 to effectively clarify the issues surrounding the independent claims, and as such, the dependent claim is now properly further limiting. Applicants respectfully request therefore, that the objection to claim 12 under §1.75(c) be withdrawn.

2.7 THE REJECTION OF CLAIMS 1-12 UNDER 35 U. S. C. § 103(A) IS OVERCOME

Claims 1-12 were rejected under 35 U. S. C. § 103(a) as allegedly being legally obvious over Chinese patent 1,163,780, either alone, or in further view of Robinson *et al.*

Applicants respectfully traverse.

However, in the interest of expedient prosecution of the pending claims to allowance, and mindful of economic concerns and patent term issues, Applicants have amended claim 1 to effectively clarify any issues concerning obviousness in view of the '780 patent, either alone, or in combination with Robinson *et al.*

2.7.1 THE REJECTION UNDER 35 U. S. C. § 103(A) IS IMPROPER AS A MATTER OF FACT

A finding of obviousness under 35 U. S. C. § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. S.Ct. 1966).

The relevant inquiry is whether the prior art suggests the invention and whether the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success *must be founded in the prior art* and not in the Applicant's disclosure (emphasis added) *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Therefore, for the cited combination of references to render the present claims legally obvious under 35 U. S. C. § 103, the references must teach or suggest, either alone or in combination, the particular claimed compositions of the present invention. Respectfully, Applicants assert that the cited references do not.

The disclosure of the '780 patent either alone or in combination with the secondary reference Robinson et al. do not teach or suggest the invention as claimed, nor do they provide any motivation to combine the two references to arrive at the present invention.

Neither of these references discloses or suggests a growth factor composition, such as that in claim 1, which comprises:

"...a polypeptide of the TGF-β superfamily other than bFGF, and a carrier comprising a vinyl pyrrolidone polymer having a molecular weight of from about 2.5 kD to about 20 kD, and a solvent selected from the group consisting of water and aqueous buffer solutions, said composition being capable of promoting angiogenesis when administered to a living subject at a site in need of such angiogenesis."

Applicants respectfully conclude that as a matter of fact, the rejection is improper, and requests that it be withdrawn.

2.7.2 THE REJECTION UNDER 35 U. S. C. § 103(A) IS IMPROPER AS A MATTER OF LAW.

Because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished over the previously cited art (either alone or in combination) Applicants further believe that, as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

Applicants urge the application of the standard held in the case of *In re Vaeck*, 20 U.S.P.Q. 1438 (Fed. Cir. 1991), in which the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) That the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and

(2) That the prior art must demonstrate a reasonable expectation of success of the invention.

Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure (emphasis added).

Furthermore, in the case of *In re* Dow Chemical Co. (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicant's disclosure.

In the instant case, however, there is neither the *suggestion* nor the *reasonable expectation of success*. Even if one could somehow postulate that one or more of the cited references might suggest one or more of the individual components of the claimed growth factor compositions, might, in an abstract sense, be *plausible*, there is certainly no teaching or suggestion as to how one would go about developing the particular growth factor compositions

as claimed in the present invention, nor is there any suggestion in the cited references, either alone or in combination, that such an approach would be successful. These references either alone or in combination do not provide the motivation or the teaching for either preparing, or using the claimed growth factor compositions.

Furthermore, Applicants submit that the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of *In re O'Farrell* (7 U. S. P. Q. 2d 1673, 1680, Fed. Cir. 1988). In *O'Farrell*, the Court held that in order for a reference or references to obviate an invention, it must be shown that the reference(s) contain(s):

(1) Detailed enabling methodology for practicing the claimed invention;

(2) A suggestion for modifying the prior art to practice the claimed invention; and

(3) Evidence suggesting that the invention would be successful.

In the present case, neither of the cited references provides any teaching relevant to the question of how one of skill in the arts would be motivated to prepare one or more of the claimed growth factor compositions, or to use them in one or more of the claimed methods.

Also in the present case, none of the cited references provides any suggestion for combining the teachings of the Chinese '780 patent and Robinson *et al.*, or for modifying any of these prior disclosures in a manner that would allow one to arrive at the present invention.

Finally, in the present case, none of the cited obviousness references provides any evidence that the particular compositions of the present invention would be successful in the claimed methods. Clearly the rejection is improper as it fails the tripartite test of *In re O'Farrell.*

Applicants assert that any combination of the cited references is, at best, merely an invitation for further experimentation in the field, and at most, an "obvious-to-try" situation.

However, there is *no* reasonable expectation of success, *nor* is there the motivation or teaching to guide a skilled artisan how to achieve such success. The Federal Circuit, in the case of *In re Geiger* (815 F.2d. 686, 2 U.S.P.Q.2d 1276, Fed. Cir. 1987), held that obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching, suggestion or incentive supporting the combination. Again, Applicants believe that the rejection fails the test of *In re Geiger.*

Further, in *Amgen v. Chugai Pharmaceutical Co. Ltd.*, (927 F. 2d 1200, 18 U.S.P.Q. 2d 1016, 1022, Fed. Cir. 1991) the Court affirmed that obviousness under 35 U. S. C. § 103 is a question of law, and that both the suggestion and the expectation of success must be founded in the prior art, and not in the Applicant's disclosure. Because the suggestion and expectation of success are absent in the cited art, Applicants assert that the rejection also fails the test of *Amgen v. Chugai Pharmaceutical Co. Ltd.*

Therefore, as a matter of both fact and law, the present Applicants believe that the obviousness rejection over the Chinese -780 patent, either alone or in combination with Robinson *et al.,* is improper and must be withdrawn.

Because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished over the previously cited art (either alone or in combination) Applicants believe that, as a matter of fact, and as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

Applicants respectfully submit that all aspects of the instant 35 U. S. C. § 103 rejections have been overcome and withdrawal of the rejections is earnestly solicited.

As discussed during the recent Examiner Interview, Applicants have also voluntarily amended the language of claims 30 and 31, to pre-empt any potential rejection of these two

claims in view of the two cited references, either alone, or in combination, for the reasons of record against claims 1-12. Applicants thus believe that all claims are free from rejection under 35 U. S. C. § 103(a), and request that the claims proceed to allowance.

2.8 CONCLUSION

Applicants believe the present paper to be a full and timely-filed response to the outstanding Action. Applicants further believe that all rejections should be withdrawn and the pending claims be advanced to allowance.

The Examiner is invited to contact the undersigned at (713) 934-4084 with any questions, comments, or suggestions relating to the referenced patent application.

Respectfully submitted,

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